Description

This invention relates to iron compounds for use in pharmaceutical compositions for the treatment of iron deficiency anaemia.

An adequate supply of iron to the body is an essential requirement for tissue growth in both man and animals. Although there is normally an ample amount of iron in the diet, the level of absorption of iron from food is generally low so that the supply of iron to the body can easily become critical under a variety of conditions. Iron deficiency anaemia is commonly encountered in pregnancy and may also present a problem in the newly born, particularly in certain animal species such as the pig. Moreover, in certain pathological conditions there is a maldistribution of body iron leading to a state of chronic anaemia. This is seen in chronic diseases such as rheumatoid arthritis, certain haemolytic diseases and cancer.

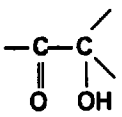
Although a wide range of iron compounds is already marketed for the treatment or iron deficiency anaemia the level of iron uptake by the body from these compounds is often quite low, necessitating the adminstration of relatively high dosage levels of the compound. The administration of high dose, poorly adsorbed, iron complexes may cause siderosis of the gut wall and a variety of side effects such as nausea, vomiting, constipation and heavy malodorous stools.

The present invention relates to a group or iron complexes which we have identified as being of particular value for use at relatively low dosage levels in the treatment of iron deficiency anaemia. Our European Patent Application Number A—0093498 describes a group of 3-hydroxypyrid-2- and -4-ones and their use in the treatment of iron overload through the formation *in vivo* of the iron complexes of these compounds. The present application relates to the use of the same iron complexes in pharmaceutical compositions for the treatment or iron deficiency anaemia.

Accordingly the present invention comprises an iron complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, for the use in therapy.

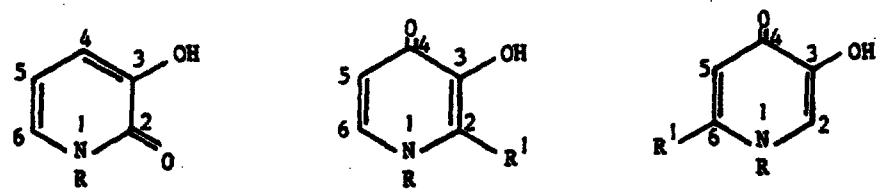
The iron complexes of use in the present invention preferably contain iron in the ferric state. Although the use of complexes containing iron in the ferrous state may be considered, such complexes tend to be less stable and are thus of less interest. The iron complexes are preferably neutral and this is conveniently achieved by complexing with a ferric cation the appropriate number of anions derived from a hydroxypyridone (through the conversion $OH \rightarrow O^-$) necessary to produce neutrality. Preferred iron complexes of use in the present invention are thus of the 3:1 form, containing three hydroxypyridone anions complexed with ferric cation, and these complexes are believed never to have been previously prepared.

The 3-hydroxypyrid-2- and -4-ones may carry more than one type of aliphatic hydrocarbon group and, in particular, the group attached to the nitrogen atom may be different from any aliphatic hydrocarbon group or groups attached to ring carbon atoms. Groups attached to carbon atoms are, however, more often the same when more than one is present. The aliphatic hydrocarbon groups, whether attached to a nitrogen or a carbon atom, may be cyclic or acyclic, having a branched chain or especially a straight chain in the latter case, and may be unsaturated or saturated. Groups of from 1 to 4 carbon atoms and particularly of 1 to 3 carbon atoms are of most interest. Saturated groups are preferred, these being either cyclic such as the cycloalkyl groups cyclopropyl and especially cyclohexyl or, more particularly, acyclic such as the alkyl groups methyl, ethyl, n-propyl and isopropyl. Where the ring carbon atoms are substituted by an aliphatic hydrocarbon group or groups these groups are preferably methyl but in the case of the group substituting the nitrogen atom larger groups may more often be utilised with particular advantage. Substitution of the ring carbon atoms, which is preferably by one rather than two or three aliphatic hydrocarbon groups, is of particular interest inn the case of the 3-hydroxypyrid-4-ones, for example at the 6- or the 2- position, whilst the 3-hydroxypyrid-2-ones may more often be used without any additional aliphatic hydrocarbon group substituent on the ring carbon atoms. Particularly if the ring carbon atoms are substituted by the larger aliphatic hydrocarbon groups, however, there may be an advantage in avoiding substitution on a carbon atom alpha to the



system. This system is involved in the complexing with iron and the close proximity of one of the larger aliphatic hydrocarbon groups may lead to steric effects which inhibit complex formation.

Examples of specific compounds whose iron complexes are of use in the present invention are shown by the following formulae (I), (II) and (III):—



(I) (II) (III)

in which R is a cycloalkyl or alkyl group, for example methyl, ethyl, n-propyl or isopropyl, and R^1 is hydrogen or a cycloalkyl or alkyl group, for example methyl.

It shold be noted that among the 3-hydroxypyrid-2-ones and 3-hydroxypyrid-4-ones, the former are of rather greater interest in the iron complex form for iron donation and the latter are of rather greater interest in the free form, as described in our co-pending application EP—A—0093498, for iron removal.

Certain of the hydroxypyridones referred to above are known compounds and, for some of these the colour reaction which they show in solution with ferric chloride has been reported in the literature but no product was characterised. Moreover, it should be noted that the procedures described do not yield a solid complex and that the prevailing conditions are such that the mixture of complexes which sould be formed in solution does not include a complex of the 3:1 form referred to hereinbefore, both the amount of ferric chloride and also the pH of the reaction mixture having an influence on the nature of the complex produced. In many cases, however, either the hydroxypyridone is novel and/or even a colour reaction with ferric chloride has not been described.

The present invention thus also includes, *per se*, the neutral 3:1 hydroxypyridone:iron (III) complexes of the 3-hydroxypyrid-2-ones and 3-hydroxypyrid-4-ones substituted by aliphatic hydrocarbon groups described hereinbefore.

The iron complexes are conveniently prepared by the reaction of the hydroxypyridone and iron ions, the latter conveniently being derived from an iron salt, particularly a ferric halide and especially ferric chloride. The reaction is conveniently effected in a suitable mutual solvent and water may often be used for this purpose. If desired, however, an aqueous/organic solvent mixture may be used or an organic solvent, for example ethanol, methanol, chloroform and mixtures of these solvents together and/or with water where appropriate. In particular, methanol or especially ethanol may be used as the solvent where it is desired to effect the separation of at least a major part of a by-product such as sodium chloride by precipitation whilst the iron complex is retained in solution.

It will be appreciated that the nature of the iron complex obtained by the reaction of a hydroxypyridone and iron ions will depend both on the proportion of these two reactants and upon the pH of the reaction medium. Thus, for the preparation of the 3:1 ferric complex, for example, the hydroxypyridone and the ferric salt are conveniently mixed in solution in a 3:1 molar proportion and pH adjusted to a value in the range of 6 to 9, for example 7 or 8. If a similar excess of hydroxypyridone:iron is employed but no adjustment is made of the acidic pH which results on the admixture of the hydroxypyridone and an iron salt such as ferric chloride then a mixture of the 2:1 and 1:1 complex will instead be obtained.

Reaction to form the iron complex is generally rapid and will usually have proceeded substantially to completion after 5 minutes at about 20°C, although a longer reaction time may be used if necessary. Following separation of any precipitated by-product, such as sodium chloride in the case of certain solvent systems, the reaction mixture may conveniently be evaporated on a rotary evaporator or freeze dried to yield the solid iron complex. This may, if desired, be crystallised from a suitable solvent, for example water, an alcohol such as ethanol, or a solvent mixture, including mixtures containing an ether. The present invention thus further includes a process for the preparation of an iron complex of a 3-hydroxypyrid-2-one for 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, which comprises reacting said hydroxypyridone with iron ions and isolating the resultant complex in solid form.

Whilst for some uses it may be appropriate to prepare the iron complex in substantially pure form, i.e. substantially free from by-products of manufacture, in other cases, for example with a solid oral formulation as described hereinafter, the presence of by-products such as sodium chloride may be quite acceptable. In general, however, the neutral 3:1 [hydroxypyridone:iron (III)] complex is of particular interest in a form free from by-products which are complexes containing different proportions of hydroxypyridone and iron, in particular the 2:1 and 1:1 complexes. Accordingly the present invention includes an iron complex, for example the 3:1 hydroxypyridone:iron (III) complex, of a 3-hydroxypyrid-2-one or 3-hydroxypyridone-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by

an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, when in a form subtantially free from iron complexes of the hydroxypyridone containing other proportions of iron. As indicated hereinafter, it may be advantageous under some circumstances for the iron complex to be used in admixture with the free hydroxypyridone and, if desired, such a mixture may be obtained directly by reacting a molar proportion of the hydroxypyridone and iron ions of greater than 3:1.

The 3-hydroxypyrid-2-one compounds may conveniently be prepared by nucleophilic substitution at the nitrogen atom of the corresponding 2,3-dihydroxypyridine, for example using an organic halide R'X in which R' represents the aliphatic hydrocarbon group present on the nitrogen atom of the desired 3-hydroxypyrid-2-one and X represents an iodo group. The 3-hydroxypyrid-4-one compounds may conveniently be prepared similarly or preferably from the more readily accessible corresponding 3-hydroxy-4-pyrone. Thus, the 3-hydroxy-4-pyrone may conveniently be converted to the 3-hydroxy-pyrid-4-one through protection of the hydroxy group, for example as an ether group such as a benzyloxy group, and reaction of the protected compound with a compound $R'NH_2$, in which R' represents the aliphatic hydrocarbon group present on the nitrogen atom of the desired 3-hydroxypyrid-4-one, in the presence of a base, for example an alkali metal hydroxide such as sodium hydroxide. The protecting group may then be removed.

It will be appreciated that these are not the only routes available to these compounds and their iron complexes and that various alternatives may be used as will be apparent to those skilled in the art.

The iron complexes, for example the neutral 3:1 hydroxypyridone:iron (III) complexes, may be formulated for use as pharmaceuticals for veterinary or human use by a variety of methods. The present invention thus includes a pharmaceutical composition comprising as an active component thereof a neutral 3:1 hydroxypyridone:iron (III) complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable diluent or carrier.

The pharmaceutical composition may, for example, incorporate water or a medium containing an organic solvent as a diluent, having the form of a solution, suspension or emulsion. Aqueous, oily or emulsified compositions incorporating a liquid diluent will, however, most usually be employed for parenteral administration and therefore may conveniently be sterile and pyrogen free. However, oral administration is generally to be preferred for the treatment of iron deficiency anaemia in humans and the complexes of the present invention may be given by such a route. Although compositions incorporating a liquid diluent may be used for oral administration, it is preferred to use compositions incorporating a solid carrier. This may, for example, be a conventional solid carrier material such as starch, lactose, dextrin or magnesium stearate, and the composition may, for example, be formed as tablets. The iron complex will of course be present in such a preferred composition in solid form and the present invention extends to an iron complex of a 3-hyroxypyrid-2-one or 3-hydroxypyrid-4-one as defined above in solid form.

In the case of animals, compositions for parenteral administration are of greater interest. The problems of iron deficiency anaemia in newly born pigs arise primarily during the first three weeks or so of their life when a very rapid weight gain takes place. The iron complexes of the present invention may be used to treat piglets directly by a parenteral route but an alternative approach is to enhance the iron content of the milk on which the piglets are feeding by treating the mother pig using oral or parenteral administration, for example with an injectable slow release preparation.

Other forms of administration than by injection or through the oral route may also be considered in both human and veterinary contexts for example the use of suppositories for human administration.

Compositions may be formulated in unit dosage form, i.e. in the form of discrete portions containing a unit dose, or a multiple or sub-unit of a unit dose. Whilst the dosage of hydroxypyridone iron complex given will depend on various factors, including the particular compound which is employed in the composition, it may be stated by way of guidance that maintenance of the amount of iron present in the human body at a satisfactory level will often be achieved using a daily dosage, in terms of the iron content of the compound, which lies in a range from about 0.1 to 100 mg and often in a range from 0.5 to 10 mg, for example 1 or 2 mg, veterinary doses being on a similar g/kg body weight ratio. However, it will be appreciated that it may be appropriate under certain circumstances to give daily dosages either below or above these levels. In general, the aim should be to provide the amount of iron required by the patient without administering any undue excess and the properties of the pharmaceutical compositions according to the present invention are particularly suited to the achievement of this aim. Where desired, an iron complex of more than one hydroxypyridone as described above may be present in the pharmaceutical composition or indeed other active compounds may be included in the composition, for example compounds having the ability to facilitate the treatment of anaemia, such as folic acid.

Although it has previously been known that certain of the hydroxypyridones referred to hereinbefore show a colour reaction on treatment with ferric chloride, it has never before been appreciated that the iron complexes of such compounds might be used, and with great advantage, in the treatment of iron deficiency anaemia. Accordingly the present invention includes the use of an iron complex of a 3-hydroxy-

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pyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, for the manufacture of a medicament for use in effecting an increase in the levels of iron in a patient's bloodstream.

We have found that the iron complexes described herein are particularly suited to the treatment of iron anaemia deficiency both in humans and also in a veterinary context, particularly for the treatment of various mammalian species and especially pigs. The complexes will partition into n-octanol indicating that they are able to permeate biological membranes, this property being confirmed in practice by tests of the ability of the ^{59}Fe labelled iron complexes to permeate erythrocytes. The measured coefficients (K_{part}) for partition of various of the compounds and their iron complexes are presented in Table 1 of Example 1 hereinafter. Although the ability of both the iron complex and the corresponding metal free compound to permeate membranes is important, it is also desirable for both to possess some degree of water solubility. Preferred iron complexes show a value of K_{part} for the complex of above 0.02 but less than 6.0, especially of above 0.2 but less than 1.0, together with a value of K_{part} for the free compound of above 0.05 but less than 3.0, especially of above 0.2 but less than 1.0. Reference to Table 1 will show that the preferences as to the structure of the compounds in compositions according to the present invention which are expressed hereinbefore lead to compounds which have K_{part} values both in the free state and as 3:1 iron complexes which are broadly in line with the ranges indicated above.

Moreover, the ability of the iron complexes of the present invention to promote iron uptake with a high level of efficiency, as compared with a range of other iron complexes currently marketed for the treatment of iron deficiency anaemia, has been confirmed by measurements in the rat small intestine. Once present in the bloodstream, the complexes will donate iron to transferrin, a position of equilibrium being set up between the complexes and transferrin. It is because of the existence of this equilibrium that the corresponding free hydroxypyridones may equally be used in the treatment of iron overload, although certain of these compounds may be of particular value for use in the free state for iron removal and others may be of particular value for use as iron complexes for iron supply. Preliminary experiments have suggested that the 3-hydroxypyrid-2-ones may be more efficient at donating iron to transferrin than the 3-hydroxypyrid-4-ones.

Certain aspects of their formulation may enhance the activity of the complexes in particular contexts. Thus, although the neutral 3:1 ferric complexes are stable over a wide pH range from about 4 or 5 up to 10, they will dissociate at the pH values of less than 4 prevailing in the stomach to form a mixture of the 2:1 and 1:1 complex together with the free hydroxypyridone. If these complexes and the free hydroxypyridone are cleared simultaneously from the stomach, when they reach the small intestine a large proportion of the 3:1 complex should reform under the alkaline conditions present therein. However, in the event that this dissociation under acid conditions leads to a significant reduction in the uptake of iron by the body, due for instance to absorption of the free hydroxypyridone through the stomach wall, the uptake may be improved by using one or more of the following procedures in the formulation of the iron complex. Firstly, one of several variations may be employed which avoid or reduce exposure of the iron complex to the acidic conditions of the stomach. Such approaches may range from a controlled release system which simply delays release of the complex, through a buffered system which avoids dissociation under acidic conditions, to a system which is biased towards release under alkaline rather than acidic conditions and thus allows optimised release under alkaline conditions such as prevail in the small intestine.

A second approach to countering the effect of the acidic conditions prevailing in the stomach is to formulate the iron complex in the pharmaceutical composition together with the metal-free hydroxypyridone from which it is derived. The dissociation of the neutral 3:1 ferric complex, for example, involves various equilibria between this complex, the 2:1 and 1:1 complexes, and the metal-free compound, so that the presence of the latter will inhibit this dissociation. Any proportion of the free compound can be advantageous in this context but little further advantage accrues from increasing the proportion beyond a certain level. A preferred range for the molar proportion of the free compound present in compositions according to the present invention is thus from 0 to 100 moles free hydroxypyridone:1 mole of iron complex, particularly the neutral 3:1 iron (III) complex. Conveniently, a proportion of up to no more than 20, 30 or 50 moles:1 mole is used with a lower level of 1 or 2 moles:1 mole, although to obtain a marked effect upon dissociation of the iron complex a proportion of at least 5 or 10 moles:1 mole is usually employed. Thus, a preferred range is from 10 moles:1 to 20 moles:1 mole. The use of such a mixture is an important feature of the present invention since it can enable one to obtain almost quantitative uptake of iron from the complex.

A further advantage than prevention of dissociation of the iron complex under acidic conditions may accrue from the use of a free hydroxypyridone in admixture with its iron complex. Thus, in certain pathological conditions there may be an excess of iron deposited at certain sites even though the patient exhibits an overall anaemia. In these patients the use of such a mixture has the advantage that the iron complex will remedy the overall anaemia whilst the free hydroxypyridone will act to remove iron from pathological to physiological sites. Moreover, there may be an advantage in formulating the iron complex of one hydroxypyridone as described herein with another one of such hydroxypyridones in free form or with a mixture of the corresponding free hydroxypyridone, present primarily to prevent dissociation of the

iron complex, and of another such hydroxypyridone in free form, present primarily to effect iron transfer. Thus, it is preferable for the hydroxypyridone present in an iron donor to be rapidly metabolized so as to effect its removal from the system once it has given up its iron at an appropriate site in the system, whilst it is preferable for a hydroxypyridone being used as an iron remover not to be rapidly metabolized so that it remains in the system, taking up iron, for an extended period. For this reason the use of different hydroxypyridones in the free form and as the iron complex has certain advantages. Moreover, different hydroxypyridones may, for other reasons, function more efficiently either in the free form as an iron remover or in complex form as an iron donor. Of some especial interest are mixtures of an iron complex of a hydroxypyrid-2-one with a free hydroxypyrid-4-one, and optionally also with the corresponding free hydroxypyrid-2-one. If desired, the free hydroxypyridone may alternatively be used in salt form.

The present invention thus includes pharmaceutical compositions as described hereinbefore containing as an active component thereof an iron complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms together with an additional active component being the same or different 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom is attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or with a salt of such a pyridone containing a physiologically acceptable cation.

When a free 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one is present in admixture with the iron complex of a 3-hydroxypyrid-4-one or 3-hydroxypyrid-2-one for the purpose of acting as an iron remover, then the amount of the former may be different than when the free hydroxypyridone necessarily corresponds to that present in the iron complex and is present primarily to prevent dissociation. Thus the daily dosage of the iron complex may be as above and the daily dosage of the free hydroxypyridone may be that quoted in our co-pending application EP—A—0 093 498, i.e. about 0.1 g to 5 g for human use, particularly 0.5 g to 2 g, from which it will be seen that the proportion of iron complex and free hydroxypyridone used in such a context may extend across a wide range but preferred amounts of the free compound tend to be higher than in the other instance. It will be appreciated that, as an alternative to combination with a different free hydroxypyridone of the same type, the iron complex may be used in combination with another iron chelating agent.

In addition to the pharmaceutical uses of the iron complexes discussed above they are also of potential interest as a source of iron in various other contexts including in cell and bacterial growth, in plant growth, as a colouring agent and in the control of iron transport across membranes.

This invention is illustrated by the following Examples.

EXAMPLES

Example 1

Preparation of the iron complexes

The iron complex of 1-ethyl-3-hydroxypyrid-2-one is prepared by either procedure (a) or procedure (b).

(a) An aqueous solution of ferric chloride is reacted for 5 minutes at room temperature with an aqueous solution containing 3 molar equivalents of 1-ethyl-3-hydroxypyrid-2-one. The resultant solution is adjusted to pH 7.0 using 2 molar aqueous sodium hydroxide and is then freeze dried. The resulting powder is extracted with chloroform, filtered and the filtrate subjected to rotary evaporation to give an essentially quantitative yield of the neutral complex containing the 1-ethyl-3-hydroxypyrid-2-one anion and the ferric cation in 3:1 proportion. Recrystallisation of the 3:1 complex from ethanol gives purple crystals, m.p. 149°—151°C, ν_{max} (nujol) 1,600, 1,540, 1,500 cm^{-1}.

(b) An ethanolic solution of ferric chloride is reacted for 5 minutes at room temperature with a chloroform solution containing 3 molar equivalents of 1-ethyl-3-hydroxypyrid-2-one. The resultant solution is neutralised by the addition of solid sodium carbonate, the precipitated sodium chloride removed by filtration and the filtrate evaporated to give an essentially quantitative yield of the 3:1 complex, m.p. 149°—151°C.

The 3:1 iron (III) complexes of the 1-methyl, 1-propyl and 1-(1'-methylethyl) derivatives of 3-hydroxypyrid-2-one and of the 1-methyl, 1-ethyl, 1-propyl, 1-(1'-methylethyl) and 1-butyl derivatives of 3-hydroxy-2-methylpyrid-4-one are prepared in an exactly similar manner, their melting points (approximated to a single figure) being respectively, 165°C, 150°C, 155°, 250°C, 270°C, 280°C, 280°C and 270°C.

When an excess (5 to 50 molar equivalents) of any pyridone is used, both procedure (a) and procedure (b) lead to an essentially quantitative yield of the excess pyridone in free form in admixture with the 3:1 complex.

The partition coefficient K_{part}, being the ratio (concentration of compound in n-octanol)/(concentration of compound in aqueous phase) on partition between n-octanol and aqueous tris hydrochloride (20 mM, pH 7.4; tris represents 2-amino-2-hydroxymethylpropane 1,3-diol), is measured at 20°C for each of the iron complexes and their corresponding iron-free compound (at 10^{-4} M) by spectrophotometry. Acid washed glassware is used throughout and, following mixing of 5 ml of the 10^{-4} M aqueous solution with 5 ml of n-octanol for 1 minute, the aqueous n-octanol mixture is centrifuged at 1,000 g for 30 seconds. The two

resulting phases are separated for a concentration determination by spectrophotometry on each. For the free hydroxypyridones, the range 220—340 nm is used for concentration determinations whilst for the iron complexes the range 340—640 nm is used.

Values typical of those obtained are shown in Table 1 where it will be seen that quite small changes in structure such as the replacement of a 1-propyl group by a 1-(1'-methylethyl) group can produce quite large differences in K_{part} values. For comparitive purposes, the K_{part} values for iron (III) EDTA and iron (III) ascorbate are 0.001 and 0.0015, respectively, which values are extremely low in relation to those for the hydroxypyridone iron complexes.

TABLE 1

Compound	Partition Coefficient, K_{part}	
	Free Compound	Iron complex $[Fe^{III}\text{-(compound)}_3]$
3-hydroxy-1-methylpyrid-2-one	0.44	0.10
1-ethyl-3-hydroxypyrid-2-one	0.52	1.06
3-hydroxy-1-propylpyrid-2-one	0.78	6.20
3-hydroxy-1-(1'-methylethyl)pyrid-2-one	3.10	13.50
3-hydroxy-1,2-dimethylpyrid-4-one	0.21	0.05
1-ethyl-3-hydroxy-2-methylpyrid-4-one	0.40	0.03
3-hydroxy-2-methyl-1-propylpyrid-4-one	0.67	0.53
3-hydroxy-1-(1'-methylethyl)-2-methylpyrid-4-one	0.95	0.20
1-butyl-3-hydroxy-2-methylpyrid-4-one	5.30	7.70

The ability of the complexes to bind haemoglobin is investigated by studying the elution profile of a ^{59}Fe label when a mixture of haemoglobin and the ^{59}Fe-labelled 3:1 (pyridone:iron) neutral complex (at 1 mM concentration) is applied to a PD—10 column [Sephadex G—10 (Trade Mark) gel permeation column — Pharmacia]. Such binding, which is undesirable, is found not to occur to any substantial extent for those complexes where K_{part} does not exceed 2, the degree of binding being proportional to the value of K_{part}.

PREPARATION OF HYDROXYPYRIDONE STARTING MATERIALS

(A) Preparation of 3-hydroxy-1-methylpyrid-2-one

2,3-Dihydroxypyridine (5.55 g) is suspended in methyl iodide (20 ml) in a sealed tube and heated for 24 hours at 140°C. The reaction is taken to be complete when a dark brown residue forms as a separate phase from the methyl iodide and the tube is then cooled in solid carbon dioxide and opened. The excess methyl iodide is poured off, distilled water (10 ml) is added to the brown residue, and sulphur dioxide gas is bubbled through the mixture until the aqueous phase becomes clear. The pH of the reaction mixture is adjusted to a value of 6 with 1 M aqueous sodium carbonate and the resulting solution then saturated with ammonium sulphate and extracted with chloroform until the chloroform layer no longer gives a blue colouration when added to ferric chloride solution. The chloroform extracts are combined and dried over sodium sulphate. The solvent is then evaporated under vacuum and the resulting residue is crystallised from petroleum ether (b.p. 100°—120°C) using activated charcoal to give 3-hydroxy-1-methylpyrid-2-one, m.p. 129°—131°C; ν_{max} (Nujol) 1,660, 3,100 cm^{-1}; δ (d_6DMSO) 3.6 (s, 3H), 6.1 (t, 1H), 6.8 (m, 2H), 7.3 (s, 1H); M^+ 125 (Nujol is a Trade Mark).

(B) Preparation of other 3-hydroxypyrid-2-ones

2,3-Dihydroxypyridine is reacted with ethyl iodide, n-propyl iodide and isopropyl iodide under similar conditions to those described in (A) for methyl iodide. The reaction mixtures are worked up as described in (A) to give the following compounds:—

1-ethyl-3-hydroxypyrid-2-one: m.p. 130°—132°C; ν_{max} (Nujol®) 1,620, 3,100 cm^{-1}; δ (d_6DMSO) 1.2 (t, 3H) 3.8 (m, 2H), 6.0 (t, 2H), 6.8 (m, 2H), 8.9 (s, 1H); M^+ 139.

3-hydroxy-1-propylpyrid-2-one: m.p. 148°C; ν_{max} (Nujol®) 1,620, 3,150 cm^{-1}; δ (d_6DMSO) 0.7 (t, 3H) 1.5 (m, 2H), 3.7 (t, 2H), 5.8 (t, 1H) 6.5—7.0 (m, 2H), 8.7 (s, 1H); M^+ 153.

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3-hydroxy-1-(1'-methylethyl)pyrid-2-one: m.p. 190°C; ν_{max} (Nujol) 1,660, 3,200 cm^{-1}; δ (d_6DMSO) 1.0 (d. 6H), 6.0 (m, 1H), 6.5 (t, 1H), 6.7 (m, 2H); M^+ 153.

(C) Preparation of 3-hydroxy-1,2-dimethylpyrid-4-one

3-Benzyloxy-2-methyl-4-pyrone

3-Hydroxy-2-methyl-4-pyrone (22.2 g) in methanol (225 ml) is added to aqueous sodium hydroxide (25 ml containing 7.5 g NaOH). Benzyl chloride (25.5 g) is added and the mixture is refluxed for 6 hours and is then allowed to cool overnight. The bulk of the methanol is removed under vacuum and the residue is treated with water (50 ml). The mixture is extracted into dichloromethane (3 × 25 ml). The extracts are combined, washed with 5% w/v NaOH (2 × 25 ml), then water (2 × 25 ml) and dried over magnesium sulphate. Evaporation of the solvent gives crude 3-benzyloxy-2-methyl-4-pyrone (35 g, 92%) which is purified by distillation in nitrogen under reduced pressure to yield a colourless oil (28 g) of b.p. 148°C/ 0.3 mbar (0.2 mm).

1,2-Dimethyl-3-benzyloxypyrid-4-one

3-Benzyloxy-2-methyl-4-pyrone (4.8 g) and methylamine hydrochloride (1.56 g) are dissolved in water (200 ml) and ethanol (100 ml) containing sodium hydroxide (2 g) is added. The mixture is stirred at room temperature for 6 days and is then acidified with concentrated hydrochloric acid to pH 2, and evaporated to dryness. The resulting colourless solid is washed with water and extracted into chloroform (2 × 50 ml). The chloroform extracts are combined, dried over magnesium sulphate, and evaporated to yield 1,2-dimethyl-3-benzyloxypyrid-4-one (3.2 g).

1,2-Dimethyl-3-hydroxypyrid-4-one

1,2-Dimethyl-3-benzyloxypyrid-4-one (2 g) is added to concentrated hydrobromic acid (10 ml) and heated on a steam bath for 30 minutes. The resulting mixture is then recrystallised from water to yield 1,2-dimethyl-3-hydroxypyrid-4-one (1 g), m.p. 230°C (with decomposition); ν_{max} (Nujol®) 1,620, 3,150 cm^{-1}; δ (d_6DMSO) 2.3 (s, 3H), 3.8 (s, 3H) 6.9 (d, 1H), 7.8 (d, 1H); M^+ 139.

(D) Preparation of other 3-hydroxypyrid-4-ones

3-Benzyloxy-2-methyl-4-pyrone is prepared as described in (C) and is reacted with ethylamine, n-propylamine, isopropylamine, n-butylamine and n-hexylamine hydrochloride under similar conditions to those described in (C) for methylamine hydrochloride. The reaction mixture is worked up and the hydroxy group deprotected as described in (C) to give the following compounds:

1-Ethyl-3-hydroxy-2-methylpyrid-4-one: m.p. 190°—195°C; ν_{max} (Nujol®) 1,620, 3,150 cm^{-1}; δ (d_6DMSO) 1.1 (t, 3H), 2.6 (s, 3H), 3.5 (m, 2H), 7.3 (d, 1H), 8.5 (d, 1H); M^+ 153.

3-Hydroxy-2-methyl-1-propylpyrid-4-one: m.p. 182°—183°C; ν_{max} (Nujol®) 1,630, 3,200 cm^{-1}; δ (d_6DMSO) 0.9 (t, 3H), 1.6 (m, 2H), 2.43 (s, 3H), 4.2 (t, 2H), 7.1 (d, 1H), 8.15 (d, 1H); M^+ 167.

3-Hydroxy-2-methyl-1-(1'-methylethyl)pyrid-4-one: m.p. 198°—200°C; ν_{max} (Nujol®) 1,630, 3,150 cm^{-1}, δ (d_6DMSO) 1.28 (d, 6H), 2.43 (s, 3H), 4.8 (m, 1H), 7.15 (d, 1H), 8.15 (d, 1H); M^+ 167.

1-Butyl-3-hydroxy-2-methylpyrid-4-one: m.p. 188°—190°C; ν_{max} (Nujol®) 1,630, 3,200 cm^{-1}, δ (d_6DMSO) 0.9 (t, 3H), 1.3 (m, 4H), 2.41 (s, 3H), 4.2 (t, 2H), 7.2 (d, 1H), 8.3 (d, 1H); M^+ 181.

1-Hexyl-3-hydroxy-2-methylpyrid-4-one: m.p. 166—168°C; ν_{max} (Nujol®) 1,630, 3,200 cm^{-1}; δ (d_6DMSO) 0.8 (t, 3H), 1.3 (m, 8H), 2.5 (s, 3H), 4.2 (t, 2H), 7.4 (d, 1H), 8.3 (d, 1H); M^+ 209.

Example 2

The ability of iron complexes to donate iron to apotransferrin

Apotransferrin (10^{-4} M) and the iron complex of 1-ethyl-3-hydroxypyrid-2-one or 1-ethyl-2-methyl-3-hydroxypyrid-4-one (10^{-4} M; prepared as described in Example 1) were incubated together in tris hydrochloride (50 mM, buffered to pH 7.4) at 37°C for a period of 1 hour. At 10, 20, 30 and 60 minute intervals 1 ml aliquots were removed from the media and added to a PD10 column. 0.5 ml fractions were collected directly into scintillation vials for counting. The ^{59}Fe associated with both the apotransferrin and the ligand was estimated as a function of time. It was found that over 90% of the iron was removed from the iron complex of 1-ethyl-3-hydroxypyrid-2-one by apotransferrin within 10 minutes, whereas with 1-ethyl-2-methyl-3-hydroxypyrid-4-one the equivalent figure was 55%. Thus, although both the 3-hydroxy-pyrid-2-ones and the 3-hydroxypryid-4-ones are able to donate iron to apotransferrin, the former are the more efficient.

Example 3

In vitro tests of iron donating ability of iron complexes

(A) Rat jejunal sac

The iron uptake into the serosal space of the inverted rat jejunal sac was compared for various iron compounds. Rats (male Sprague Dawley, 60 g) were killed and the jejenum removed, everted and cut into three segments (4 cm length). The segments were tied at both ends and filled with Krebs Ringer buffer (0.2 ml) and incubated in Krebs Ringer buffer containing ^{59}Fe complexes at 37°C for periods up to 1 hour. The contents of the sac were counted for ^{59}Fe and measured spectrophotometrically.

The results obtained for 5 of the iron complexes described in Example 1 and for 7 other iron compounds which are each contained in preparations marketed for the treatment of iron deficiency anaemia are shown in Table 2, the iron uptake for each compound being shown relative to that for ferric chloride as 1. It will be seen that the complexes of Example 1 each provide a level of iron uptake which is significantly higher than the levels observed for any of the 7 compounds in current use for the treatment or iron deficiency anaemia.

TABLE 2

Compound	Relative Iron Uptake	Compound	Relative Iron Uptake
$FeCl_3$	1	$FeCl_3$	1
Fe^{III} complex of:		Fe^{II} sulphate	2.4
3-hydroxy-1-methylpyrid-2-one	36	Fe^{II} fumarate	4.0
1-ethyl-3-hydroxypyrid-2-one	37	Fe^{II} gluconate	1.6
3-hydroxy-1-propylpyrid-2-one	34	Fe^{II} succinate	2.0
3-hydroxy-1-(1'-methylethyl)-pyrid-2-one	27	Fe^{III} EDTA Fe^{III} ascorbate	3.6 0.4
3-hydroxy-1,2-dimethylpyrid-4-one	30	Fe^{III} citrate	2.0

(B) Human erythrocytes The accumulation of iron by human erythrocytes which are associated with various of the iron complexes described in Example 1 was studied by incubating for 1 hour at 37°C a 5% suspension of erythrocytes in a medium consisting of the ^{59}Fe labelled iron complex (10^{-3} M) in aqueous sodium chloride (130 mM) buffered to pH 7.4 by tris hydrochloride (2 ml). Following this period of incubation, an aliquot of the erythrocyte/medium mixture was placed above a layer of silicone oil and the erythrocytes separated by centrifugation through the oil. The ^{59}Fe levels associated with the erythrocytes and the incubation medium were then counted. The results obtained are shown in Table 3 where the amount of the complex entering erythrocytes (n.mole) is given the quoted values being in each case the mean of at least three determinations.

It will be seen that the uptake of the complexes at 1 hour shows a clear relationship with their K_{part} values quoted in Example 1, thereby indicating that a non-facilitative process is involved. The concentrations above 500 n.mole are due to binding of haemoglobin, which is not a desired property, so that, from this point of view, compounds listed in the Table with a figure of less than 250 are of especial interest.

Table 3

Compound	Amount of complex entering erythrocytes (n.mole)
Fe^{III} complex of:	
3-hydroxy-1-methylpyrid-2-one	60
1-ethyl-3-hydroxypyrid-2-one	250
3-hydroxy-1-propylpyrid-2-one	710
3-hydroxy-1-(1'-methylethyl)-pyrid-2-one	770
3-hydroxy-1,2-dimethylpyrid-4-one	25
1-ethyl-3-hydroxy-2-methylpyrid-4-one	20
3-hydroxy-2-methyl-1-propylpyrid-4-one	53
3-hydroxy-1-(1'-methylethyl)-2-methylpyrid-4-one	22
1-butyl-3-hydroxy-2-methylpyrid-4-one	1630

Example 4

In vivo study of the permeability of cat intestine towards iron complexes

The action of the iron complex of 1-ethyl-3-hydroxypyrid-2-one, prepared as described in Example 1, was compared with that of iron (III) EDTA (1:1 molar ratio) which is one of the iron compounds currently marketed for the treatment of iron deficiency anaemia. Two cats (ca 2.7 kg) were anaethetised and a solution in aqueous tris hydrochloride (20 mM, pH 7.4) of ^{59}Fe labelled complex (1 ml of solution with an iron concentration of 1 mg/1 ml) was administered directly into the small intestine, one cat receiving iron (III) 1-ethyl-3-hydroxypyrid-2-one, in the presence of a 20-fold excess of metal-free 1-ethyl-3-hydroxypyrid-2-one, and the other receiving iron (III) EDTA. The blood levels of ^{59}Fe were recorded as a function of time, the results being shown in Table 4, and both cats were then killed after 4 hours. The total ^{59}Fe present in the kidneys and urine was then measured in each case. The percentage of the total dose in the kidneys and urine was 1.6% and 21%, respectively, for the iron (III) EDTA indicating that this complex is cleared rapidly into the urine. For the iron (III) 1-ethyl-3-hydroxypyrid-2-one, however, 0.05% of the total dose was found in the kidneys and no more than 0.01% in the urine, clearance in this manner therefore being very slow for this complex.

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TABLE 4

Time after administration of complex (minutes)	Concentration of [^{59}Fe] in blood (c.p.m.)	
	iron pyridone complex	iron EDTA complex
20	200	226
40	475	352
60	643	414
80	661	434
100	784	340
120	870	400
140	834	460
160	750	532
180	900	500
240	948	472

As well as the kidneys, various other tissues of the cat which received the Fe(III) 1-ethyl-3-hydroxy-pyrid-2-one were studied to assess the percentage of the original ^{59}Fe dose which was present. The results are shown in Table 5 and it will be seen that the iron, rather than being excreted in the urine, is instead widely distributed throughout the body. Furthermore, when this neutral complex was injected intravenously it was cleared from the circulation with a half life of 45 minutes. The tissue distribution after intravenous injection was found to be similar to that resulting from the intrajejunal infusion, these results also being reported in Table 5, from which it will be seen that in this instance less than 1% of the dose appears in the urine. The bulk of the dose given by either route is estimated to be in the reticuloendothelial system (bone marrow). This was confirmed by the identification of high levels of ^{59}Fe in the sternum. Over 95% of the ^{59}Fe present in the blood after 1 hour was bound to transferrin and thus would be expected to be mainly directed to the reticuloendothelial system.

TABLE 5

Tissue	Percentage of original ^{59}Fe dose after 4 hours	
	intrajejunal	intravenous
Blood	3	7
Liver	1.6	5.3
Kidneys	0.05	1
Spleen	0.1	0.7
Heart	1.5	1.1
Skeletal Muscle	0.8	0.5
Intestinal Tissue	30	—
Urine	0.01	0.5
Reticuloendothelial System (Bone Marrow)	ca 60	ca 80

Claims

1. An iron complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, for use in therapy.

2. A complex according to Claim 1, being a neutral 3:1 hydroxypyridone:iron(III) complex.

3. A neutral 3:1 hydroxypyridone:iron(III) complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms.

4. A complex according to Claim 3 in solid form.

5. A complex according to any of Claims 1 to 4, in which the or each aliphatic hydrocarbon group is of 1 to 4 carbon atoms.

6. A complex according to any of Claims 1 to 5, in which the or each aliphatic hydrocarbon group is a cycloalkyl or alkyl group.

7. A complex according to any of Claims 1 to 6, in which the or each aliphatic hydrocarbon group is an acyclic group.

8. A complex according to any of Claims 1 to 4, in which the hydrogen atom attached to the nitrogen atom and, optionally, also one or more of the hydrogen atoms attached to ring carbon atoms are replaced by the same or a different substituent selected from the group consisting of methyl, ethyl, n-propyl and isopropyl.

9. A complex according to any of Claims 1 to 8, in which the hydrogen atom attached to the nitrogen atom and, optionally, also one of the hydrogen atoms attached to ring carbon atoms are replaced.

10. A complex according to any of Claims 1 to 9, in which any replacement of a hydrogen atom attached to a ring carbon atom is effected by a methyl group.

11. A complex according to any of Claims 1 to 10, in which the pyridone is a 3-hydroxypyrid-2-one.

12. A complex according to Claim 11, in which the 3-hydroxypyrid-2-one is substituted only on the nitrogen atom.

13. A complex according to any of Claims 1 to 10, in which the pyridone is a 3-hydroxypyrid-4-one substituted on the nitrogen atom and by a single additional substituent at the 2- or 6-position.

14. A complex according to any of Claims 1 to 4, in which the pyridone is 3-hydroxy-1-methylpyrid-2-one, 1-ethyl-3-hydroxypyrid-2-one, 3-hydroxy-1-propylpyrid-2-one, 3-hydroxy-1-(1'-methylethyl)-pyrid-2-one, 3-hydroxy-1,2-dimethylpyrid-4-one, 1-ethyl-3-hydroxy-2-methylpyrid-4-one, 3-hydroxy-2-methyl-1-propylpyrid-4-one or 3-hydroxy-1-(1'-methylethyl)-2-methylpyrid-4-one.

15. A complex according to any of Claims 1 to 4, in which the pyridone is 1-ethyl-3-hydroxypyrid-2-one, 3-hydroxy-1-propylpyrid-2-one or 3-hydroxy-1-(1'-methylethyl)-pyrid-2-one.

16. A mixture of an iron complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the

TABLE 5

Tissue	Percentage of original ^{59}Fe dose after 4 hours	
	intrajejunal	intravenous
Blood	3	7
Liver	1.6	5.3
Kidneys	0.05	1
Spleen	0.1	0.7
Heart	1.5	1.1
Skeletal Muscle	0.8	0.5
Intestinal Tissue	30	—
Urine	0.01	0.5
Reticuloendothelial System (Bone Marrow)	ca 60	ca 80

Claims

1. An iron complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, for use in therapy.

2. A complex according to Claim 1, being a neutral 3:1 hydroxypyridone:iron(III) complex.

3. A neutral 3:1 hydroxypyridone:iron(III) complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms.

4. A complex according to Claim 3 in solid form.

5. A complex according to any of Claims 1 to 4, in which the or each aliphatic hydrocarbon group is of 1 to 4 carbon atoms.

6. A complex according to any of Claims 1 to 5, in which the or each aliphatic hydrocarbon group is a cycloalkyl or alkyl group.

7. A complex according to any of Claims 1 to 6, in which the or each aliphatic hydrocarbon group is an acyclic group.

8. A complex according to any of Claims 1 to 4, in which the hydrogen atom attached to the nitrogen atom and, optionally, also one or more of the hydrogen atoms attached to ring carbon atoms are replaced by the same or a different substituent selected from the group consisting of methyl, ethyl, n-propyl and isopropyl.

9. A complex according to any of Claims 1 to 8, in which the hydrogen atom attached to the nitrogen atom and, optionally, also one of the hydrogen atoms attached to ring carbon atoms are replaced.

10. A complex according to any of Claims 1 to 9, in which any replacement of a hydrogen atom attached to a ring carbon atom is effected by a methyl group.

11. A complex according to any of Claims 1 to 10, in which the pyridone is a 3-hydroxypyrid-2-one.

12. A complex according to Claim 11, in which the 3-hydroxypyrid-2-one is substituted only on the nitrogen atom.

13. A complex according to any of Claims 1 to 10, in which the pyridone is a 3-hydroxypyrid-4-one substituted on the nitrogen atom and by a single additional substituent at the 2- or 6-position.

14. A complex according to any of Claims 1 to 4, in which the pyridone is 3-hydroxy-1-methylpyrid-2-one, 1-ethyl-3-hydroxypyrid-2-one, 3-hydroxy-1-propylpyrid-2-one, 3-hydroxy-1-(1'-methylethyl)-pyrid-2-one, 3-hydroxy-1,2-dimethylpyrid-4-one, 1-ethyl-3-hydroxy-2-methylpyrid-4-one, 3-hydroxy-2-methyl-1-propylpyrid-4-one or 3-hydroxy-1-(1'-methylethyl)-2-methylpyrid-4-one.

15. A complex according to any of Claims 1 to 4, in which the pyridone is 1-ethyl-3-hydroxypyrid-2-one, 3-hydroxy-1-propylpyrid-2-one or 3-hydroxy-1-(1'-methylethyl)-pyrid-2-one.

16. A mixture of an iron complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the

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hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms together with a different 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or with a salt of such a different pyridone containing a physiologically acceptable cation.

17. A mixture according to Claim 16, in which the complexed pyridone is a 3-hydroxypyrid-2-one and the uncomplexed pyridone is a 3-hydroxypyrid-4-one.

18. A mixture according to Claim 16 or 17, in which the iron complex is a neutral 3:1 hydroxypyridone:iron(III) complex.

19. A mixture according to Claim 18, which additionally contains the same pyridone, in uncomplexed form, as is present in the iron complex, or a salt thereof containing a physiologically acceptable cation.

20. A mixture of a neutral 3:1 hydroxypyridone:iron(III) complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms together with the same 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in uncomplexed form, or a salt thereof containing a physiologically acceptable cation.

21. A pharmaceutical composition comprising as an active component thereof a neutral 3:1 hydroxypyridone:iron(III) complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable diluent or carrier.

22. A pharmaceutical composition comprising as an active component thereof an iron complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable solid carrier.

23. A pharmaceutical composition according to Claim 22 which is adapted for oral administration.

24. A pharmaceutical composition according to Claim 22 in suppository form.

25. A pharmaceutical composition comprising as an active component thereof an iron complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable liquid diluent, the composition being of sterile injectable form.

26. A pharmaceutical composition comprising as an active component thereof an iron complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, together with a physiologically acceptable diluent or carrier, the composition being of delayed release form.

27. A pharmaceutical composition according to Claim 26 in a form biased towards release under alkaline rather than acidic conditions.

28. A pharmaceutical composition according to any of Claims 21 to 27 in unit dosage form.

29. A pharmaceutical composition according to any of Claims 22 to 28 in which the complex is a neutral 3:1 hydroxypyridone:iron(III) complex.

30. A pharmaceutical composition according to Claim 21 or 29, in which the neutral 3:1 complex is substantially free from complexes containing other proportions of pyridone and iron(III).

31. A pharmaceutical composition according to any of Claims 21 to 30, in which the iron complex is in substantially pure form.

32. A pharmaceutical composition according to any of Claims 21 to 31, in which the or each aliphatic hydrocarbon group is of 1 to 4 carbon atoms.

33. A pharmaceutical composition according to any of Claims 21 to 32, in which the or each aliphatic hydrocarbon group is a cycloalkyl or alkyl group.

34. A pharmaceutical composition according to any of Claims 21 to 33, in which the or each aliphatic hydrocarbon group is an acyclic group.

35. A pharmaceutical composition according to any of Claims 21 to 31, in which the hydrogen atom attached to the nitrogen atom and, optionally, also one or more of the hydrogen atoms attached to ring carbon atoms are replaced by the same or different substituents selected from the group consisting of methyl, ethyl, n-propyl and isopropyl.

36. A pharmaceutical composition according to any of Claims 21 to 35, in which the hydrogen atom

attached to the nitrogen atom and, optionally, also one of the hydrogen atoms attached to ring carbon atoms are replaced.

37. A pharmaceutical composition according to any of Claims 21 to 36, in which any replacement of a hydrogen atom attached to a ring carbon atom is effected by a methyl group.

38. A pharmaceutical composition according to any of Claims 21 to 36, in which the pyridone is a 3-hydroxypyrid-2-one.

39. A pharmaceutical composition according to Claim 38, in which the 3-hydroxypyrid-2-one is substituted only on the nitrogen atom.

40. A pharmaceutical composition according to any of Claims 21 to 37, in which the pyridone is a 3-hydroxypyrid-4-one substituted on the nitrogen atom and by a single additional substituent at the 2- or 6-position.

41. A pharmaceutical composition according to any of Claims 21 to 31, in which the pyridone is 3-hydroxy-1-methylpyrid-2-one, 1-ethyl-3-hydroxypyrid-2-one, 3-hydroxy-1-propylpyrid-2-one, 3-hydroxy-1-(1'-methylethyl)-pyrid-2-one, 3-hydroxy-1,2-dimethylpyrid-4-one, 1-ethyl-3-hydroxy-2-methylpyrid-4-one, 3-hydroxy-2-methyl-1-propylpyrid-4-one or 3-hydroxy-1-(1'-methylethyl)-2-methylpyrid-4-one.

42. A pharmaceutical composition according to any of Claims 21 to 41 which contains an iron chelating agent as an additional active component thereof.

43. A pharmaceutical composition according to Claim 42, in which the iron chelating agent is an uncomplexed 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or a salt thereof containing a physiologically acceptable cation.

44. A pharmaceutical composition according to Claim 43, in which the uncomplexed pyridone is a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one as defined in any of Claims 32 to 41.

45. A pharmaceutical composition according to Claim 43 or 44 which contains a complexed pyridone together with the same pyridone in uncomplexed form, or a salt thereof containing a physiologically acceptable cation.

46. A pharmaceutical composition according to any of Claims 21 to 45 which contains folic acid as an additional active component thereof.

47. A process for the preparation of an iron complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, which comprises reacting said hydroxypyridone with iron ions and isolating the resultant complex in solid form.

48. The use of an iron complex of a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, for the manufacture of a medicament for use in effecting an increase in the levels of iron in a patient's bloodstream.

Patentansprüche

1. Eisenkomplex eines 3-Hydroxypyrid-2-ons oder 3-Hydroxypyrid-4-ons; bei dem das an das Stickstoffatom angefügte Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist und bei dem gegebenenfalls ein oder mehrere der an die Ringkohlenstoffatome angefügten Wasserstoffatome ebenfalls durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, zur Verwendung in der Therapie.

2. Komplex nach Anspruch 1, dadurch gekennzeichnet, daß er ein neutraler 3:1-Hydroxypyridon:Eisen(III)-Komplex ist.

3. Neutraler 3:1-Hydroxypyridon:Eisen(III)-Komplex eines 3-Hydroxypyrid-2-ons oder 3-Hydroxypyrid-4-ons, bei dem das an das Stickstoffatom angefügte Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist und bei dem gegebenenfalls ein oder mehrere der an die Ringkohlenstoffatome angefügten Wasserstoffatome ebenfalls durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind.

4. Komplex nach Anspruch 3 in fester Form.

5. Komplex nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß die oder jede aliphatische Kohlenwasserstoffgruppe 1 bis 4 Kohlenstoffatome aufweist.

6. Komplex nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß die oder jede aliphatische Kohlenwasserstoffgruppe eine Cycloalkyl- oder Alkylgruppe ist.

7. Komplex nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß die oder jede aliphatische Kohlenwasserstoffgruppe eine acyclische Gruppe ist.

8. Komplex nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß das an das Stickstoffatom angefügte Wasserstoffatom und gegebenenfalls auch ein oder mehrere der an die Ringkohlenstoffatome angefügten Wasserstoffatome durch den gleichen oder einen verschiedenen Substituenten, ausgewählt aus der Gruppe bestehend aus Methyl, Ethyl, n-Propyl und Isopropyl, ersetzt sind.

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9. Komplex nach einem der Ansprüche 1 bis 8, dadurch gekennzeichnet, daß das an das Stickstoffatom angefügte Wasserstoffatom und gegebenenfalls auch eines der an Ringkohlenstoffatome angefügten Wasserstoffatome ersetzt sind.

10. Komplex nach einem der Ansprüche 1 bis 9, dadurch gekennzeichnet, daß irgendein Ersatz eines an ein Ringkohlenstoffatom angefügten Wasserstoffatoms durch eine Methylgruppe bewirkt worden ist.

11. Komplex nach einem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß das Pyridon 3-Hydroxypyrid-2-on ist.

12. Komplex nach Anspruch 11, dadurch gekennzeichnet, daß das 3-Hydroxypyrid-2-on nur auf dem Stickstoffatom substituiert ist.

13. Komplex nach einem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß das Pyridon 3-Hydroxypyrid-4-on ist, welches auf dem Stickstoffatom und durch einen einzigen zusätzlichen Substituenten in 2- oder 6-Stellung substituiert ist.

14. Komplex nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß das Pyridon 3-Hydroxy-1-methylpyrid-2-on, 1-Ethyl-3-hydroxypyrid-2-on, 3-Hydroxy-1-propylpyrid-2-on, 3-Hydroxy-1-(1'-methylethyl)-pyrid-2-on, 3-Hydroxy-1,2-dimethylpyrid-4-on, 1-Ethyl-3-hydroxy-2-methylpyrid-4-on, 3-Hydroxy-2-methyl-1-propylpyrid-4-on oder 3-Hydroxy-1-(1'-methylethyl)-2-methylpyrid-4-on ist.

15. Komplex nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß das Pyridon 1-Ethyl-3-hydroxypyrid-2-on, 3-Hydroxy-1-propylpyrid-2-on oder 3-Hydroxy-1-(1'-methylethyl)-pyrid-2-on ist.

16. Gemisch aus einem Eisenkomplex eines 3-Hydroxypyrid-2-ons oder 3-Hydroxypyrid-4-ons, bei dem das an das Stickstoffatom angefügte Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist und bei dem gegebenenfalls ein oder mehrere der an die Ringkohlenstoffatome angefügten Wasserstoffatome ebenfalls durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, mit einem davon verschiedenen 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, bei dem das an das Stickstoffatom angefügte Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist und bei dem gegebenenfalls ein oder mehrere der an die Ringkohlenstoffatome angefügten Wasserstoffatome ebenfalls durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, oder mit einem Salz eines derartigen davon verschiedenen Pyridons, das ein physiologisch annehmbares Kation enthält.

17. Gemisch nach Anspruch 16, dadurch gekennzeichnet, daß das in Komplexform vorliegende Pyridon ein 3-Hydroxypyrid-2-on ist und daß das nicht in Komplexform vorliegende Pyridon ein 3-Hydroxypyrid-4-on ist.

18. Gemisch nach Anspruch 16 oder 17, dadurch gekennzeichnet, daß der Eisenkomplex ein neutraler 3:1-Hydroxypyridon:Eisen(III)-Komplex ist.

19. Gemisch nach Anspruch 18, dadurch gekennzeichnet, daß es weiterhin das gleiche Pyridon in einer nicht im Komplex vorliegenden Form, wie es in dem Eisenkomplex vorhanden ist, oder ein Salz davon, das ein physiologisch annehmbares Kation enthält, enthält.

20. Gemisch aus einem neutralen 3:1-Hydroxypyridon:Eisen(III)-Komplex eines 3-Hydroxypyrid-2-ons oder 3-Hydroxypyrid-4-ons, bei dem das an das Stickstoffatom angefügte Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist und bei dem gegebenenfalls ein oder mehrere der an die Ringkohlenstoffatome angefügten Wasserstoffatome ebenfalls durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, zusammen mit dem gleichen 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on in einer nicht im Komplex vorliegenden Form oder einem Salz davon, das ein physiologisch annehmbares Kation enthält.

21. Pharmazeutische Zusammensetzung, dadurch gekennzeichnet, daß sie als wirksame Komponente einen neutralen 3:1-Hydroxypyridon:Eisen(III)-Komplex eines 3-Hydroxypyrid-2-ons oder 3-Hydroxypyrid-4-ons, bei dem das an das Stickstoffatom angefügte Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist und bei dem gegebenenfalls ein oder mehrere der an die Ringkohlenstoffatome angefügten Wasserstoffatome ebenfalls durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, zusammen mit einem physiologisch annehmbaren Verdünnungsmittel oder Träger, enthält.

22. Pharmazeutische Zusammensetzung, dadurch gekennzeichnet, daß sie als wirksame Komponente einen Eisenkomplex eines 3-Hydroxypyrid-2-ons oder 3-Hydroxypyrid-4-ons, bei dem das an das Stickstoffatom angefügte Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist und bei dem gegebenenfalls ein oder mehrere der an die Ringkohlenstoffatome angefügten Wasserstoffatome ebenfalls durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, zusammen mit einem physiologisch annehmbaren festen Träger, enthält.

23. Pharmazeutische Zusammensetzung nach Anspruch 22, dadurch gekennzeichnet, daß sie für die orale Verabreichung ausgebildet ist.

24. Pharmazeutische Zusammensetzung nach Anspruch 22 in Form von Suppositorien.

25. Pharmazeutische Zusammensetzung, dadurch gekennzeichnet, daß sie als wirksame Komponente einen Eisenkomplex eines 3-Hydroxypyrid-2-ons oder 3-Hydroxypyrid-4-ons, bei dem das an das Stickstoffatom angefügte Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist und bei dem gegebenenfalls ein oder mehrere der an die Ringkohlenstoffatome

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angefügten Wasserstoffatome ebenfalls durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, zusammen mit einem physiologisch annehmbaren flüssigen Verdünnungsmittel enthält, wobei die Zusammensetzung in steriler injizierbarer Form vorliegt.

26. Pharmazeutische Zusammensetzung, dadurch gekennzeichnet, daß sie als wirksame Komponente einen Eisenkomplex eines 3-Hydroxypyrid-2-ons oder 3-Hydroxypyrid-4-ons, bei dem das an das Stickstoffatom angefügte Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist und bei dem gegebenenfalls ein oder mehrere der an die Ringkohlenstoffatome angefügten Wasserstoffatome ebenfalls durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, zusammen mit einem physiologisch annehmbaren Verdünnungsmittel oder Träger enthält, wobei die Zusammensetzung in Retardform vorliegt.

27. Pharmazeutische Zusammensetzung nach Anspruch 26, dadurch gekennzeichnet, daß sie in einer Form vorliegt, welche nach einer Freisetzung unter alkalischen anstelle von sauren Bedingungen gerichtet ist.

28. Pharmazeutische Zusammensetzung nach einem der Ansprüche 21 bis 27 in Dosiseinheitsform.

29. Pharmazeutische Zusammensetzung nach einem der Ansprüche 22 bis 28, dadurch gekennzeichnet, daß der Komplex ein neutraler 3:1-Hydroxypyridon:Eisen(III)-Komplex ist.

30. Pharmazeutische Zusammensetzung nach Anspruch 21 oder 29, dadurch gekennzeichnet, daß der neutrale 3:1-Komplex im wesentlichen von Komplexen frei ist, die andere Verhältnismengen von Pyridon und Eisen(III) enthalten.

31. Pharmazeutische Zusammensetzung nach einem der Ansprüche 21 bis 30, dadurch gekennzeichnet, daß der Eisenkomplex in im wesentlichen reiner Form vorliegt.

32. Pharmazeutische Zusammensetzung nach einem der Ansprüche 21 bis 31, dadurch gekennzeichnet, daß die oder jede aliphatische Gruppe 1 bis 4 Kohlenstoffatome aufweist.

33. Pharmazeutische Zusammensetzung nach einem der Ansprüche 21 bis 32, dadurch gekennzeichnet, daß die oder jede aliphatische Kohlenwasserstoffgruppe eine Cycloalkyl- oder Alkylgruppe ist.

34. Pharmazeutische Zusammensetzung nach einem der Ansprüche 21 bis 33, dadurch gekennzeichnet, daß die oder jede aliphatische Kohlenwasserstoffgruppe eine acyclische Gruppe ist.

35. Pharmazeutische Zusammensetzung nach einem der Ansprüche 21 bis 31, dadurch gekennzeichnet, daß das an das Stickstoffatom angefügte Wasserstoffatom und gegebenenfalls auch ein oder mehrere der an die Ringkohlenstoffatome angefügten Wasserstoffatome durch die gleichen oder verschiedenen Substituenten, ausgewählt aus der Gruppe bestehend aus Methyl, Ethyl, n-Propyl und Isopropyl, ersetzt sind.

36. Pharmazeutische Zusammensetzung nach einem der Ansprüche 21 bis 35, dadurch gekennzeichnet, daß das an das Stickstoffatom angefügte Wasserstoffatom und gegebenenfalls auch eines der an die Ringkohlenstoffatome angefügten Wasserstoffatome ersetzt worden sind.

37. Pharmazeutische Zusammensetzung nach einem der Ansprüche 21 bis 36, dadurch gekennzeichnet, daß irgendein Ersatz eines an ein Ringkohlenstoffatom angefügten Wasserstoffatoms durch eine Methylgruppe bewirkt worden ist.

38. Pharmazeutische Zusammensetzung nach einem der Ansprüche 21 bis 36, dadurch gekennzeichnet, daß das Pyridon ein 3-Hydroxypyrid-2-on ist.

39. Pharmazeutische Zusammensetzung nach Anspruch 38, dadurch gekennzeichnet, daß das 3-Hydroxypyrid-2-on nur auf dem Stickstoffatom substituiert ist.

40. Pharmazeutische Zusammensetzung nach einem der Ansprüche 21 bis 37, dadurch gekennzeichnet, daß das Pyridon ein 3-Hydroxypyrid-4-on ist, das auf dem Stickstoffatom und durch einen einzigen weiteren Substituenten in 2- oder 6-Stellung substituiert ist.

41. Pharmazeutische Zusammensetzung nach einem der Ansprüche 21 bis 31, dadurch gekennzeichnet, daß das Pyridon 3-Hydroxy-1-methylpyrid-2-on, 1-Ethyl-3-hydroxypyrid-2-on, 3-Hydroxy-1-propylpyrid-2-on, 3-Hydroxy-1-(1'-methylethyl)-pyrid-2-on, 3-Hydroxy-1,2-dimethylpyrid-4-on, 1-Ethyl-3-hydroxy-2-methylpyrid-4-on, 3-Hydroxy-2-methyl-1-propylpyrid-4-on oder 3-Hydroxy-1-(1'-methylethyl)-2-methylpyrid-4-on ist.

42. Pharmazeutische Zusammensetzung nach einem der Ansprüche 21 bis 41, dadurch gekennzeichnet, daß sie ein Eisen-Chelierungsmittel als weitere wirksame Komponente enthält.

43. Pharmazeutische Zusammensetzung nach Anspruch 42, dadurch gekennzeichnet, daß das Eisen-Chelierungsmittel ein nicht in Komplexform vorliegendes 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, bei dem das an das Stickstoffatom angefügte Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist und bei dem gegebenenfalls ein oder mehrere der an die Ringkohlenstoffatome angefügten Wasserstoffatome ebenfalls durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, oder ein Salz davon, das ein physiologisch annehmbares Kation enthält, ist.

44. Pharmazeutische Zusammensetzung nach Anspruch 43, dadurch gekennzeichnet, daß das nicht in Komplexform vorliegende Pyridon ein 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on nach einem der Ansprüche 32 bis 41 ist.

45. Pharmazeutische Zusammensetzung nach Anspruch 43 oder 44, dadurch gekennzeichnet, daß es ein in Komplexform vorliegendes Pyridon zusammen mit dem gleichen nicht in Komplexform

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vorliegenden Pyridon oder einem Salz davon, das ein physiologisch annehmbares Kation enthält, enthält.

46. Pharmazeutische Zusammensetzung nach einem der Ansprüche 21 bis 45, dadurch gekennzeichnet, daß sie Folsäure als weitere wirksame Komponente enthält.

47. Verfahren zur Herstellung eines Eisenkomplexes eines 3-Hydroxypyrid-2-ons oder 3-Hydroxypyrid-4-ons, bei dem das an das Stickstoffatom angefügte Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist und bei dem gegebenenfalls ein oder mehrere der an die Ringkohlenstoffatome angefügten Wasserstoffatome ebenfalls durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, dadurch gekennzeichnet, daß man das genannte Hydroxypyridon mit Eisenionen umsetzt und den resultierenden Komplex in fester Form isoliert.

48. Verwendung eines Eisenkomplexes eines 3-Hydroxypyrid-2-ons oder 3-Hydroxypyrid-4-ons, bei dem das an das Stickstoffatom angefügte Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist und bei dem gegebenenfalls ein oder mehrere der an die Ringkohlenstoffatome angefügten Wasserstoffatome ebenfalls durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt sind, zur Herstellung eines Arzneimittels zur Verwendung für die Bewirkung einer Erhöhung des Eisenspiegels im Blutstrom eines Patienten.

Revendications

1. Complexe de fer d'une 3-hydroxypyrid-2-one ou d'une 3-hydroxypyrid-4-one, dans laquelle l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, dans laquelle un ou plusieurs des atomes d'hydrogène fixés sur des atomes de carbone de noyaux sont également remplacés par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, destiné à servir en thérapie.

2. Complexe selon la revendication 1, qui est un complexe neutre à 3:1 d'hydroxypyridone:fer(III).

3. Complexe neutre à 3:1 d'hydroxypyridone:fer(III) d'une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one dans laquelle l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, dans laquelle un ou plusieurs des atomes d'hydrogène fixés sur des atomes de carbone du noyau sont également remplacés par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone.

4. Complexe selon la revendication 3, sous forme solide.

5. Complexe selon l'une quelconque des revendications 1 à 4, dans lequel le ou chaque groupe hydrocarboné aliphatique comporte 1 à 4 atomes de carbone.

6. Complexe selon l'une quelconque des revendications 1 à 5, dans lequel le ou chaque groupe hydrocarboné aliphatique est un groupe cycloalkyle ou alkyle.

7. Complexe selon l'une quelconque des revendications 1 à 6, dans lequel le ou chaque groupe hydrocarboné aliphatique est un groupe acyclique.

8. Complexe selon l'une quelconque des revendications 1 à 4, dans lequel l'atome d'hydrogène fixé à l'atome d'azote et, éventuellement, aussi un ou plusieurs des atomes d'hydrogène fixés à des atomes de carbone de noyau sont remplacés par le même substituant ou par un substituant différent, choisi dans l'ensemble constitué par un groupe méthyle, éthyle, n-propyle et isopropyle.

9. Complexe selon l'une quelconque des revendications 1 à 8, dans lequel l'atome d'hydrogène fixé à l'atome d'azote et, éventuellement, également l'un des atomes d'hydrogène fixés à des atomes de carbone de noyau sont remplacés.

10. Complexe selon l'une quelconque des revendications 1 à 9, dans lequel tout remplacement éventuel d'un atome d'hydrogène fixé à un atome de carbone de noyau est réalisé par un groupe méthyle.

11. Complexe selon l'une quelconque des revendications 1 à 10, dans lequel la pyridone est une 3-hydroxypyrid-2-one.

12. Complexe selon la revendication 1, dans lequel la 3-hydroxypyrid-2-one est substituée seulement sur l'atome d'azote.

13. Complexe selon l'une quelconque des revendications 1 à 10, dans lequel la pyridone est une 3-hydroxypyrid-4-one substituée sur l'atome d'azote et par un seul substituant supplémentaire en position 2 ou 6.

14. Complexe selon l'une quelconque des revendications 1 à 4, dans lequel la pyridone est la 3-hydroxy-1-méthylpyrid-2-one, la 1-éthyl-3-hydroxypyrid-2-one, la 3-hydroxy-1-propylpyrid-2-one, la 3-hydroxy-1-(1'-méthyléthyl)-pyrid-2-one, la 3-hydroxy-1,2-diméthylpyrid-4-one, la 1-éthyl-3-hydroxy-2-méthylpyrid-4-one, la 3-hydroxy-2-méthyl-1-propylpyrid-4-one ou la 3-hydroxy-1-(1'-méthyléthyl)-2-méthylpyrid-4-one.

15. Complexe selon l'une quelconque des revendications 1 à 4, dans lequel la pyridone est la 1-éthyl-3-hydroxypyrid-2-one, la 3-hydroxy-1-propylpyrid-2-one ou la 3-hydroxy-1-(1'-méthyléthyl)-pyrid-2-one.

16. Mélange d'un complexe de fer d'une 3-hydroxypyrid-2-one ou d'une 6-hydroxpyrid-4-one, dans laquelle l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, dans laquelle 1 ou plusieurs des atomes d'hydrogène fixés sur des atomes de carbone de noyau sont également remplacés par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, avec une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one différente dans laquelle l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe

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hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, dans laquelle 1 ou plusieurs des atomes d'hydrogène fixés sur des atomes de carbone de noyau sont également remplacés par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, ou avec un sel d'une telle pyridone différente contenant un cation physiologiquement acceptable.

17. Mélange selon la revendication 16, dans lequel la pyridine complexée est une 3-hydroxypyrid-2-one et la pyridone non complexée est une 3-hydroxypyrid-4-one.

18. Mélange selon la revendication 16 ou 17, dans lequel le complexe de fer est un complexe neutre à 3:1 hydroxypyridone:fer(III).

19. Mélange selon la revendication 18, qui contient en outre la même pyridone, sous forme non complexée, que celle présente dans le complexe de fer, ou un de ses sels contenant un cation physiologiquement acceptable.

20. Mélange d'un complexe neutre à 3:1 hydroxypyridone:fer(III) dérivant d'une 3-hydroxypyrid-2-one ou d'une 3-hydroxypyrid-4-one dans laquelle l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, dans laquelle un ou plusieurs des atomes d'hydrogène fixés sur des atomes de carbone de noyau sont également remplacés par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, avec la même 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one sous forme non complexée, ou un de ses sels contenant un cation physiologiquement acceptable.

21. Composition pharmaceutique comprenant, à titre de composant actif, un complexe neutre à 3:1 hydroxypyridone:fer(III) dérivant d'une 3-hydroxypyrid-2-one ou d'une 3-hydroxypyrid-4-one dans laquelle l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, dans laquelle un ou plusieurs des atomes d'hydrogène fixés à des atomes de carbone de noyau sont également remplacés par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, avec un diluant ou excipient physiologiquement acceptable.

22. Composition pharmaceutique comprenant, à titre de composant actif, un complexe de fer d'une 3-hydroxypyrid-2-one ou d'une 3-hydroxypyrid-4-one dans laquelle l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, dans laquelle un ou plusieurs des atomes d'hydrogène fixés à des atomes de carbone de noyau sont également remplacés par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, avec un excipient solide physiologiquement acceptable.

23. Composition pharmaceutique selon la revendication 22, qui est destinée à une administration orale.

24. Composition pharmaceutique selon la revendication 22, sous forme de suppositoires.

25. Composition pharmaceutique comprenant, à titre de composant actif, un complexe de fer d'une 3-hydroxypyrid-2-one ou d'une 3-hydroxypyrid-4-one dans laquelle l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, dans laquelle un ou plusieurs des atomes d'hydrogène fixés sur des atomes de carbone de noyau sont également remplacés par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, avec un diluant liquide physiologiquement acceptable, la composition étant sous forme stérile injectable.

26. Composition pharmaceutique comprenant, à titre de composant actif, un complexe de fer d'une 3-hydroxypyrid-2-one ou d'une 3-hydroxypyrid-4-one, dans laquelle l'atome d'hydrogène fixe à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, dans laquelle un ou plusieur des atomes d'hydrogène fixés sur des atomes de carbone de noyau sont également remplacés par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, avec un diluant ou excipient physiologiquement acceptable, la composition étant sous forme à libération retardée.

27. Composition pharmaceutique selon la revendication 26, sous une forme dirigée vers une libération dans des conditions alcalines plutôt que dans des conditions acides.

28. Composition pharmaceutique selon l'une quelconque des revendications 21 à 27, sous forme de dose unitaire.

29. Composition pharmaceutique selon l'une quelconque des revendications 22 à 28, dans laquelle le complexe est un complexe neutre à 3:1 hydroxypyridone:fer III).

30. Composition pharmaceutique selon la revendication 21 ou 29, dans laquelle le complexe neutre à 3:1 est pratiquement dépourvu de complexes contenant d'autres proportions de la pyridone et du fer(III).

31. Composition pharmaceutique selon l'une quelconque des revendications 21 à 30, dans laquelle le complexe de fer est sous forme pratiquement pure.

32. Composition pharmaceutique selon l'une quelconque des revendications 21 à 31, dans laquelle le ou chaque groupe hydrocarboné aliphatique comporte 1 à 4 atomes de carbone.

33. Composition pharmaceutique selon l'une quelconque des revendications 21 à 32, dans laquelle le ou chaque groupe hydrocarboné aliphatique est un groupe cycloalkyle ou alkyle.

34. Composition pharmaceutique selon l'une quelconque des revendications 21 à 33, dans laquelle le ou chaque groupe hydrocarboné aliphatique est un groupe acyclique.

35. Composition pharmaceutique selon l'une quelconque des revendications 21 à 31, dans laquelle l'atome d'hydrogène est fixé à l'atome d'azote et, éventuellement, également un ou plusieurs des atomes d'hydrogène fixés à des atomes de carbone du noyau sont remplacés par des substituants, identiques ou

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différents, choisis dans l'ensemble constitué par un groupe méthyle, éthyle, n-propyle et isopropyle.

36. Composition pharmaceutique selon l'une quelconque des revendications 21 à 35, dans laquelle l'atome d'hydrogène fixé à l'atome d'azote et, éventuellement, aussi un des atomes d'hydrogène fixé à des atomes de carbone de noyau sont remplacés.

37. Composition pharmaceutique selon l'une quelconque des revendications 21 à 36, dans laquelle un remplacement quelconque d'un atome d'hydrogène fixé à un atome de carbone de noyau est réalisé par un groupe méthyle.

38. Composition pharmaceutique selon l'une quelconque des revendications 21 à 36, dans laquelle la pyridone est une 3-hydroxypyrid-2-one.

39. Composition pharmaceutique selon la revendication 38, dans laquelle la 3-hydroxypyrid-2-one n'est substituée que sur l'atome d'azote.

40. Composition pharmaceutique selon l'une quelconque des revendications 21 à 37, dans laquelle la pyridone est une 3-hydroxypyrid-4-one substituée sur l'atome d'azote et par un seul substituant supplémentaire en position 2 ou 6.

41. Composition pharmaceutique selon l'une quelconque des revendications 21 à 31, dans laquelle la pyridone est la 3-hydroxy-1-méthylpyrid-2-one, la 1-éthyl-3-hydroxypyrid-2-one, la 3-hydroxy-1-propylpyrid-2-one, la 1-hydroxy-(1'-méthyléthyl)-pyrid-2-one, la 3-hydroxy-1,2-diméthylpyrid-4-one, la 1-éthyl-3-hydroxy-2-méthylpyrid-4-one, la 3-hydroxy-2-méthyl-1-propylpyrid-4-one ou la 3-hydroxy-1-(1'-méthyléthyl)-2-méthylpyrid-4-one.

42. Composition pharmaceutique selon l'une quelconque des revendications 21 à 41, qui contient, à titre de composant actif supplémentaire, un agent de chélation du fer.

43. Composition pharmaceutique selon la revendication 42, dans laquelle l'agent de chélation du fer est une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one non complexée, dans lesquelles l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, dans lesquelles un ou plusieurs des atomes d'hydrogène fixé sur les atomes de carbone de noyau sont également remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, ou un de ses sels contenant un cation physiologiquement acceptable.

44. Composition pharmaceutique selon la revendication 43, dans laquelle la pyridone non complexée est une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one telle que définie dans l'une quelconque des revendications 32 à 41.

45. Composition pharmaceutique selon la revendication 43 ou 44, qui contient une pyridone complexée ainsi que la même pyridone sous forme non complexée, ou un de leurs sels contenant un cation physiologiquement acceptable.

46. Composition pharmaceutique selon l'une quelconque des revendications 21 à 45, qui contient de l'acide folique comme composant actif supplémentaire.

47. Procédé pour la préparation d'un complexe de fer d'une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one dans lesquelles l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, dans lesquelles un ou plusieurs des atomes d'hydrogène fixés sur des atomes de carbone de noyau sont également remplacés par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, qui comprend la réaction de ladite hydroxypyridone avec des ions fer et l'isolement du complexe résultant sous forme solide.

48. Utilisation d'un complexe de fer d'une 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one, dans lesquelles l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, dans lesquelles un ou plusieurs des atomes d'hydrogène fixés à des atomes de carbone de noyau sont également remplacés par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, pour la fabrication d'un médicament destiné à réaliser une augmentation des taux de fer dans le courant sanguin d'un patient.